Mangalore **University**

DESIGN AND SYNTHESIS OF BIOLOGICALLY ACTIVE THIAZOLE, THIAZOLIDINONE AND THIAZOLIDINEDIONE SCAFFOLDS: *IN SILICO* AND *IN VITRO* STUDIES

Final-synopsis

OF THE Ph.D. THESIS TO BE SUBMITTED TO THE

MANGALORE UNIVERSITY

FOR THE AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

BIOCHEMISTRY

By

UWABAGIRA NADINE

DEPARTMENT OF BIOCHEMISTRY

MANGALORE UNIVERSITY

MANGALAGANGOTHRI-574 199

KARNATAKA, INDIA.

August, 2020

Name of the Candidate	:Uwabagira Nadine
Name of the Guide	:Prof. Dr. B. K. Sarojini
Title of the Thesis	:Design and Synthesis of Biologically Active Thiazole, Thiazolidinone and Thiazolidinedione Scaffolds: *In silico* and *In vitro* Studies
Registration No. & Date	:MU/EXB/Ph.D./CR.25/Biochem./2019-20/A3 dated 11.07.2019.
Date of Joining	:05/09/2016
Place of Work	:Department of Biochemistry Mangalore University Mangalagangothri-574 199 Karnataka, India.

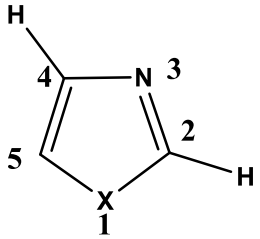
SYNOPSIS

Introduction

Heterocyclic compounds have been worked on for the past many decades due to their huge importance and occurrence in the nature. Thiamines (vitamin B1) are among naturally occurring heterocyclics. Thiamine is composed of pyrimidine ring connected with thiazole ring by the means of methylene bridge.

Thiazole was first synthesized by Hantzsch and Waber in 1887 [1]. Popp confirmed its structure in 1889 [2]. Thiazoles belong to class of organic compounds which contain 5 membered heterocyclic ring nucleus with nitrogen and sulphur atoms at 1,3 positions. Thiazole rings are planar and exhibit aromatic property which is characterised by delocalisation of π-electrons. Thiazole exhibits interesting biological activities which depend on substitution pattern on the ring [3]. Thiazoles are often used with their benzene derivatives which are commonly known as benzothiazoles. Thiazoles are found in many biologically active molecules like Sulfathiazol (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) with trade name Abasol cream, Bleomycine and Tiazofurin (antineoplastic drug) [4]. In recent years the biological application of thiazoles improved remarkably and find their uses in the treatment of allergies [5], hypertension [6], inflammation [7], schizophrenia [8], bacterial [9], HIV infections [10], hypnotics [11] etc. Many thiazole derivatives also find various applications in drug development for the treatment of cardiotonic [12], fungicidal [13], HIV infection [14], mental retardation in children, age related and neurodegenerative brain damage (Alzheimer's disease, Parkinsonism disease) [15-18].

Thiazole ring is analogous to imidazole ring where the pyrrole nitrogen is replaced by sulphur atom. The following is heterocyclic structure with X being NH (imidazole) and S (thiazole).



Both of molecules are planar and isosteric. Despite the structural identity, they differ in their reactivity. The remarkable example is in proton affinity at 3-N atom, indicated by the

experimental pKa values in water for conjugate NH acids: imidazole, 7.1 [19] and thiazole, 2.52 [20]. Thiazole is considered as aromatic, and bromination is easy for imidazole (at 2-C), somewhat more difficult for thiazole (at 5-C). The rate of alkylation at the nitrogen (3-N) decreases in the order of imidazole and thiazole as ratio of 900:15 respectively [20] in line with the decrease of the pKa. The electrophilic attack in imidazole is preferentially at nitrogen (1-N); electrophilic substitution is also seen at 5-C and 4-C, never at 2-C [21]. The electrophiles attack thiazole at 5-C, nucleophilic is rare (at 2-C). The most marked features of these two molecules appear to be the proton affinity and much different character of 5-C and 2-C positions. However, the imidazole NH proton is slightly acidic [20] (pKa = 14.52). Thiazolidinones are derivatives of thiazolidine with a keto group at 4^{th} position. Thiazolidinones scaffolds are reviewed extensively in literature for their vibrant activities such as antibacterial [22], antifungal [23], antioxidant [24], cytotoxic [25], analgesic, anti-inflammatory [26, 27], anticonvulsant [28], anti YFV (yellow fever virus) [29], anti-HIV [30] and anti-tubercular [31] and antiviral activities [32] etc.

The 2,4-thiazolidinedione derivatives are the derivative of thiazolidine scaffolds which also possess diverse biological properties such as antibacterial, antifungal, antiviral, antitumor and antidiabetic activities. Thiazolidinedione (TZD) or Rosiglitazones were found to possess oral hypoglycemic activity. They act mainly by increasing tissue sensitivity especially adipose tissue, to insulin [33]. Hence, 1,3-thiazole, thiazolidinone and 2,4-thiazolidinedione chemistry invites interest to explore them for potent biological properties.

Objectives of the study

By reviewing the latest state-of-the-art literature, the following lists of specific objectives have been formed:

- To synthesize novel moieties of thiazole, thiazolidinone and thiazolidinedione derivatives.
- To characterize the newly synthesized derivatives by IR, ^{1}H NMR, ^{13}C NMR, Mass spectra and XRD studies.
- To derive the *in silico* biological activities of all synthesized compounds by Molecular docking studies.
- To carry out *in vitro* biological activities such as antibacterial, anti-inflammatory and anticancer activities.
- To perform *in vivo* anticancer activity for some potent compounds.

The thesis entitled "**Design and synthesis of biologically active thiazole, thiazolidinone and thiazolidinedione scaffolds: *in silico* and *in vitro* studies**" has been divided into the following six chapters.

Chapter 1: A brief review on chemistry and biological activities of some thiazole, thiazolidinone and thiazolidinedione derivatives.

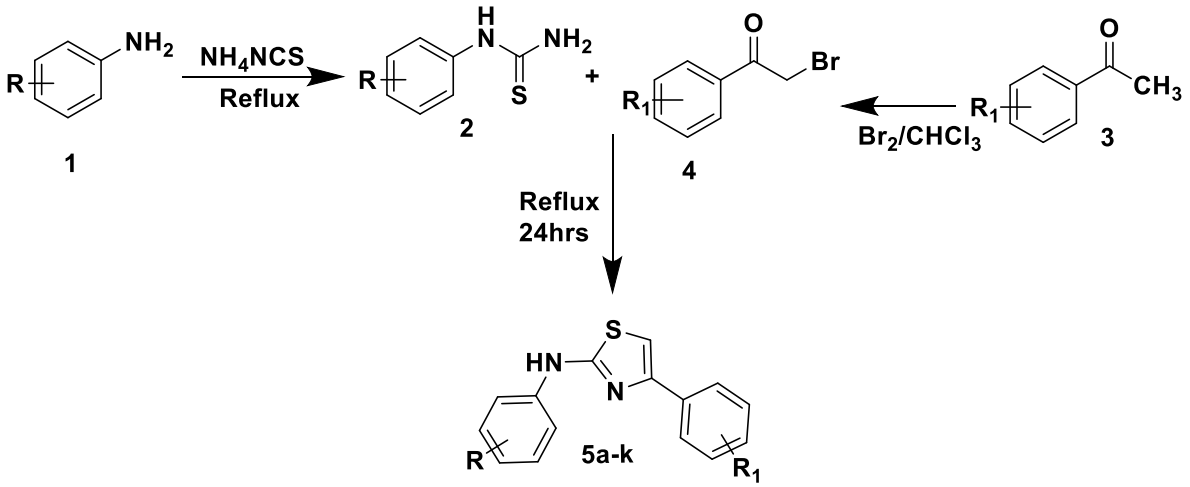
This is an introductory chapter, which deals with a brief account of synthesis and applications of some thiazole, thiazolidinone and thiazolidinedione scaffolds from the publications on chemical literature up to the year 2019.

Chapter 2: Synthesis and characterization of new thiazole derivatives

This chapter describes the synthesis and characterization of new aminothiazole derivatives.

The synthetic strategy for the preparation of the target compounds **(5a-k)** is depicted in **Scheme 2.1.** The key intermediate, substituted phenylthiourea **2** was obtained from the reaction of ammonium thiocyanate on substituted aniline derivative **1** in concentrated HCl under reflux condition [36]. The substituted 4-phenacylbromides **4** were prepared by bromination of respective acetophenones **3** in chloroform solvent [37]. The new series of substituted phenyl thiazol-2-amine **5a–k** was synthesized by refluxing a mixture of substituted phenylthiourea derivatives **2** and 4-substituted phenacylbromides **4** in ethanol in the absence of any catalyst. The formation of the title compounds **5a–k** was confirmed by their analytical and spectral data.

All the compounds were characterized by elemental analyses, IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques.



Scheme 2.1: Synthetic strategy of aminothiazole derivatives (5a-k)

Reagents and conditions: HCl, NH_4NCS, reflux, EtOH, Substituted phenacylbromide (1 equiv) reflux at 80 °C.

Chapter 3: Synthesis and characterization of new thiazolidinone derivatives

This chapter describes the synthesis and characterization of some new thiazolidinone derivatives.

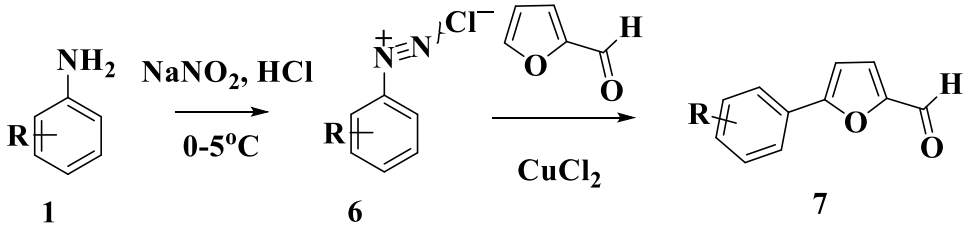
The synthetic strategy for the preparation of new thiazolidinone derivatives **(10a-f)** is depicted in **Scheme 3.1** and **3.2**.

The synthetic route for the unreported title compounds **(10a-f)** is outlined in **Scheme 3.2**. The required 5-(substituted aryl) furfural **(7)** were synthesized by the Merwein arylation of furfural with arenediazonium salts **(6)** [38]. The latter intermediate compounds (**7**) were in turn prepared by diazotization of anilines with nitrous acid produced in situ by the reaction between sodium nitrite with concentrated hydrochloric acid **(Scheme 3.1)** [39, 40]

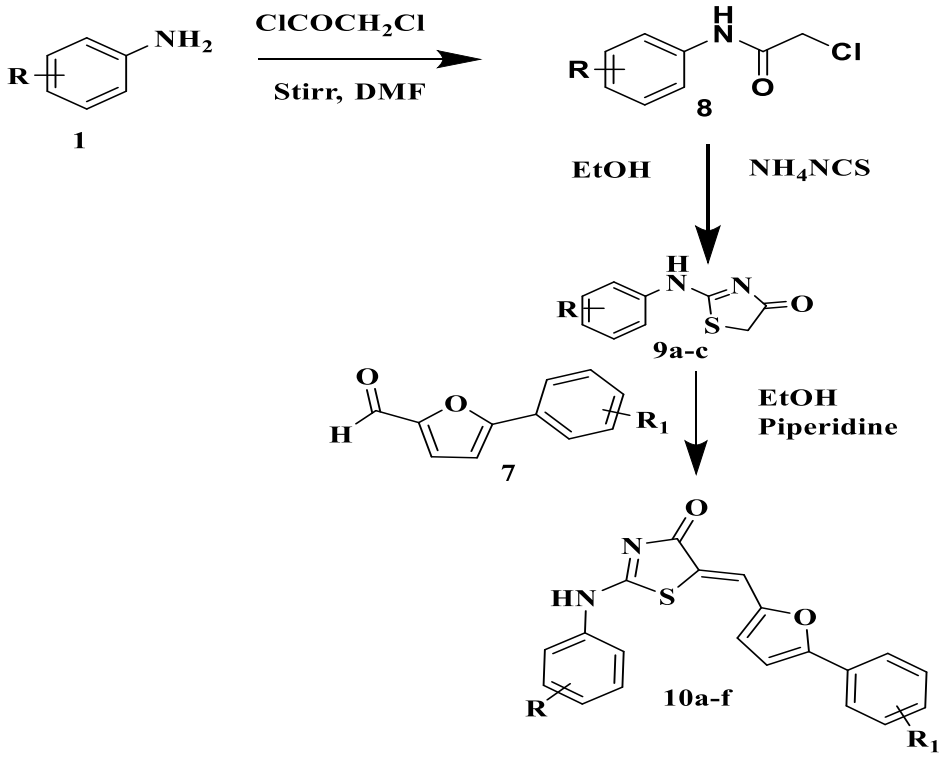
When anilinothiazolidinones (**9**) were reacted with 5-(substituted aryl) furfural **(7)** under Knoevenagel condensation condition, new series of thiazolidinone derivatives were afforded (**10a-f**) **(Scheme 3.2)**.

Reagents and conditions: Aniline, 2-chloroacetyl chloride in EtOH (1.1 equiv), 80 °C, formaldehyde (1equiv), reflux, anilinothiazolidinone and the compound (7) under Knoevenagel condensation, KOH.

All the compounds were characterized by elemental analyses, IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques.



Scheme 3.1: Synthesis of aryl furfurals



Scheme 3.2: Synthetic strategy for the preparation of thiazolidinone derivatives (10a-f)

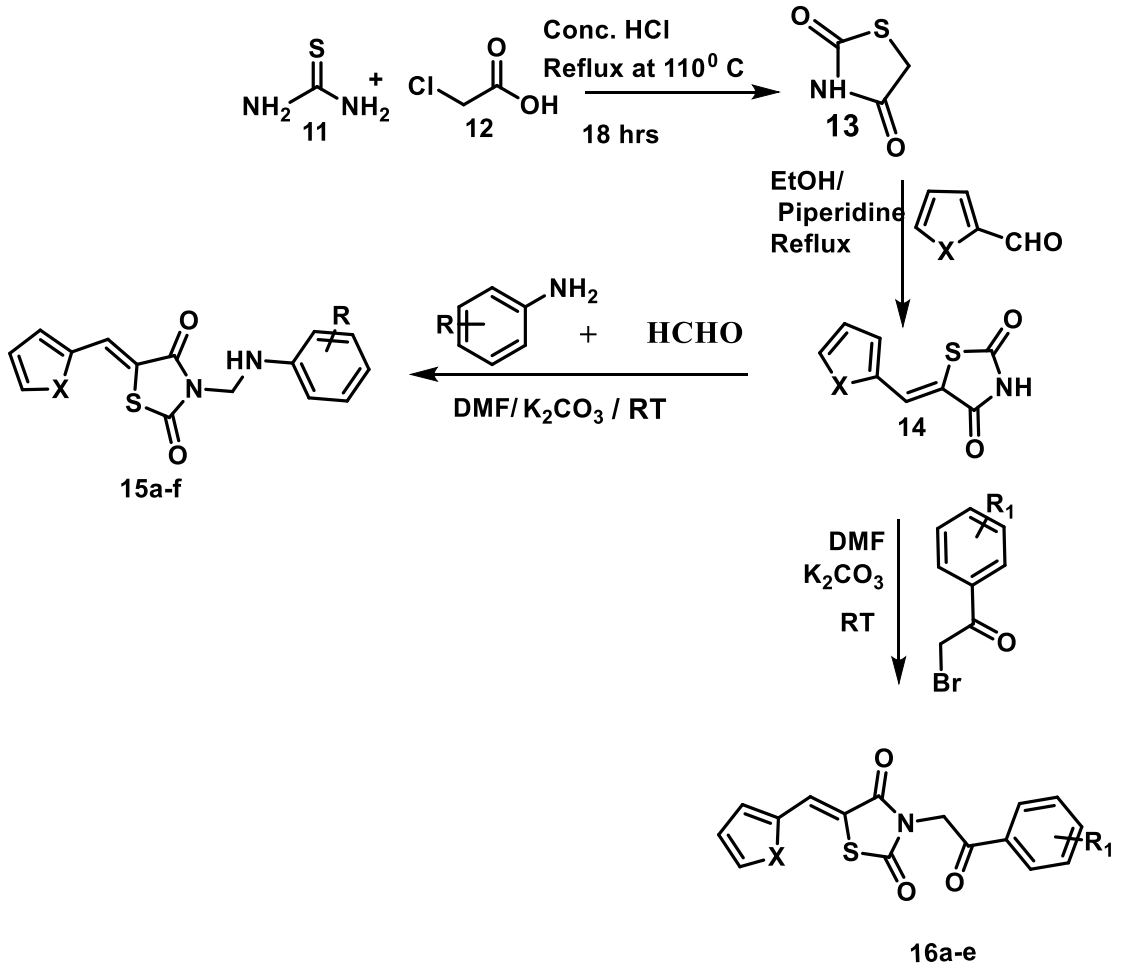
Chapter 4: Synthesis and characterization of new thiazolidinedione derivatives

This chapter describes the synthesis and characterization of some new thiazolidinedione derivatives.

The synthetic route for the unreported title compounds **15a-f** and **16a-e** which is thiazolidinedione derivatives is given in **(Scheme 4.1)**.

The reaction of thiourea **11** with 2-chloroacetic acid **12** in the presence of HCl under reflux condition at 110 ℃ for 18 hours gave thiazolidine-2,4 dione **13**. The starting material **14** was obtained by base catalyzed condensation of thiazolidinedione **13** with thiophen-2-carboldehyde/ furfural [39]. The compound **14** was dissolved in DMF (20mL) and K_2CO_3 (0.02 mol) was added, the reaction mixture was stirred continuously for 30 min at room temperature. To this, a mixture of 1.5 mL of formaldehyde (40%) and primary amines (0.01 mole) was added slowly and stirred for additional 20 minutes. The reaction yielded Manich bases **15a-f** [40]. Simiraly, compounds **16a-e** were obtained by adding substituted phenacylbromides instead of formaldehydes and primary amines to get N-substituted products **16a-e**. The products were recrystallized from methanol [41].

The structures of the newly synthesized compounds **(15a-f** and **16a-e)** were confirmed on the basis of analytical and spectral data.



Scheme 4.1: Synthetic strategy for the preparation of thiazolidinedione derivatives (15a-f and **16a-e)**

Chapter 5: *In silico* evaluation of newly synthesized compounds

To understand the interaction of all the synthesized compounds, the molecular docking studies were performed using the GLIDE (Grid-based Ligand Docking with Energetics) program (Schrödinger software). To analyse the docking results and execute the protocol, the maestro user (Schrödinger software) was employed. The PDB ID was selected for docking studies as a reference sample and was prepared for docking through a protein preparation wizard.

The docking studies were done at Mangalore University on Intel i5 powered Acer Version Workstations, Small Molecule Drug Discovery Suite 2017-1, Schrodinger, LLC, New York,

2017 are used. The synthesized compounds were docked in the active site of the *E. coli* FabH (PDB: 2VBA) for aminothiazole derivatives and Cyclin Dependent Kinase 2 (CDK2) for thiazolidinone and thiazolidinedione derivatives. The mentioned proteins were obtained from Protein Data Bank (PDB). The docking process was processed as follows: From PDB, the *E. coli* FabH (PDB: 2VBA) or CDK 2 (PDB: 3QQK), was imported into the Maestro interface, minimized, using Protein Preparation Wizard. Prime was used for filling the missing loops and missing side chains. Heterogeneous states at pH 7.0±2 were generated using Epik. All the synthesized compounds along with the inhibitor either phenylamino-4-methyl-5-acetylthiazole or **(**[4-amino-2- (prop-2-en-1-ylamino)-1,3-thiazol-5-yl] (phenyl) methanone) were prepared using Ligprep. The grid was generated by Receptor grid generation. All prepared ligands were docked into the Glide; Extra Precision (XP) was used. Many interactions were seen such as Hydrogen bonds, π-π stacking, aromatic-Hydrogen, π-cation as well as hydrophobic interactions.

The compounds to be docked were first drawn in Chembl by Chembl Draw Ultra 11.0 tool, imported in Maestro 9.0.211 (mae. format).

Ligand Preparation

The application where a simple 2D structure is converted to 3D structure is called ligand preparation (ligPrep) and this application includes the tautomeric generation, ionisation and streochemical variations. With the help of ligPrep, generated 3D structure will be accurate model [42]. The prepared ligands were minimized under the applied OPLS_2005 force field to retain the conformers with least potential energy (negative) [43].

Protein Preparation

From Protein Data Bank (PDB) (http://www.pdb.org), Protein preparation (ProPre) with PDB: 3QQK or 2VBA) was processed by protein preparation wizard (OPLS_2005). Except the wanted chains, the unwanted water, molecules, hetero atoms and residues were deleted. PDB-CASTp and Q-site finder [44] were used to identify the active site of the used proteins.

Grid generation

To carry out ligand docking, the specific active site of the protein is needed and is shown by receptor grid generation. To generate the grid, module glide is used. Grid generation also defines the receptor, positional constraints and grid generation calculations monitoring [45].

Ligand docking

The synthesized ligands along with the inhibitor were docked in the active site of the specific protein in the module GLIDE 5.0 version in the extra precision (XP) mode for accurate and clear details along with Epik state penalties to docking scores. The docking of each ligand along with the grid was carried out to generate conformational changes with the respect to the active site of the protein. The docking scores of the docked ligands were given**.** The ligands showing the least glide score are assumed to have best score and were taken for *in vitro* biological activities. Among the novel synthesized compounds, some of them showed higher interactions and docking energy more than the standard inhibitor. After docking, the Root Mean Square Deviation (RMSD) was obtained. The RMSD determines the stability of the molecules and that stability should be less than 2 to be meaningful. The binding models as well as the ligand interaction diagrams of the potent compounds are shown in the results.

Computational models are able to mimic biological processes and environment thus helping to predict the compound behaviour in cells or within the body. With computer-based study on a property of a molecule, right drug can be obtained. However, *in silico* studies only give a preliminary overview on how chemical might act in the body but unable to predict the drug behaviour. Computational biology and bioinformatics play great responsibility in designing drug molecules thus bringing much of acceleration up to the drug discovery process. Molecular docking of the target (receptor) with the ligands (drug molecules) emphasize the significant information about drug receptor interactions and is frequently used to find out the binding orientation of the protein target by the drug candidates in order to predict the drug affinity and activity.

The modern drug discovery strategies cover ligand based drug design (LBDD) and structure based drug design (SBDD) techniques to find out a compound as drug candidate. Usually, drug discovery starts from the simplest environment (i.e. biochemical assays) and lasts with more complex models. For each step, the researcher has to decide whether to proceed, stop and to reconsider. The strengths and the weaknesses of each stage should be taken into

consideration. Each step of drug discovery has its bright and dark side to show how data misleading and misinterpretation can result in failure. In the course of this study, the focus on structure based drug design technique was done with the help of Schrödinger software. The main objective was to understand how the ligand binds to the active site of the target protein based on specific interaction between ligands and proteins. Then final goal of this process was to synthesize the potential bioactive ligands as well as conducting biological activities.

Based on the above mentioned facts regarding the pharmacological importance of thiazole, thiazolidinone and thiazolidinedione scaffolds and due to the fact that novel series of biologically active compounds are highly required for the treatment of multi-drug resistant infectious diseases, it was envisioned to synthesize some aminothiazole, thiazolidinone and thiozolidinedione scaffolds and investigate their biological properties. From protein data bank (PDB), specific proteins have been chosen. The *E. coli* FabH (PDB: 2VBA) was taken for aminothiazole derivatives and CDK2 (PDB: 3QQK) was taken for thiazolidinone and thiazolidinedione derivatives.

The *E. coli β*-ketoacyl-ACP synthase (KAS) I which contributes to thiolactomycin resistance in *E. coli* was inhibited by the synthesized thiazoles especially the compound **5a** as shown by *in silico* results. This enzyme is essential for bacterial survival as it is involved in fatty acid biosynthesis.

Generally, **Cys-Hie-Asn triad tunnel** is the catalytic active site of FabH. Since this triad is conserved in bacteria and plays a significant role in chain elongation regulation and substrate binding, any interaction between the said triad and substrate revealed an important role in substrate-binding. The potency of the compounds is explained by their interactions with **Cys^{112}**, **Hie^{244}** or **Asn^{247}** residues of the proteins FabH. Studies on *E. coli* FabH confirmed that **Hie^{244}** and **Asn^{247}** are required for decarboxylation and **Cys^{112}** is essential in transacylation.

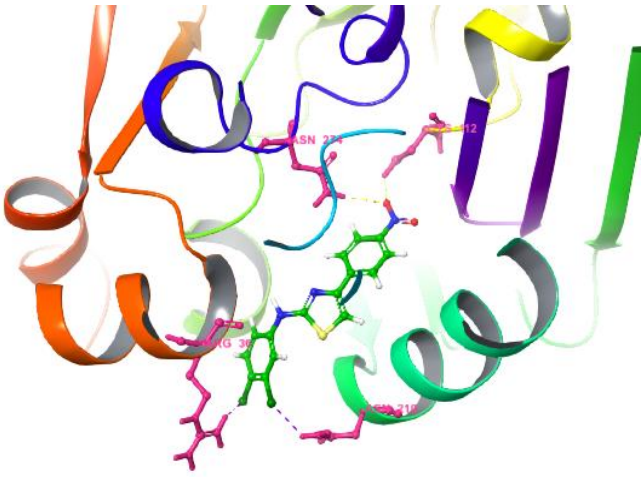


Figure 1: Docking Pose of 5a on beta-ketoacyl-ACP synthase I (KAS) for *E. coli* (ecFabH)

Since some of the compounds were having interactions with **Hie**^{244} or **Asn**^{247}; this may explain their potency on acetyl-CoA carboxylase as they are required in decarboxylation of the mentioned protein.

To predict the most possible interactions of unreported thiazolidinone derivatives, the docking was performed with the cyclin dependent kinase 2 (CDK2). As explained earlier, this protein was obtained from protein data bank (PDB) and the PDB ID: 3QQK.

The synthesized compounds inhibit the activity of the protein CDK 2 (PDB ID: 3QQk).

The compounds **10c**, **10e**, **15a**, **15b** and **16d** in addition to many interactions, they specifically interact with **Leucine** (Leu), **Isoleucine** (Ile) and **Valine** (Val) amino acids which are the branched-chain amino acids (BCAA) and the inhibition of these amino acid chains (BCAA) have been taken into consideration for their anticancer involvement.

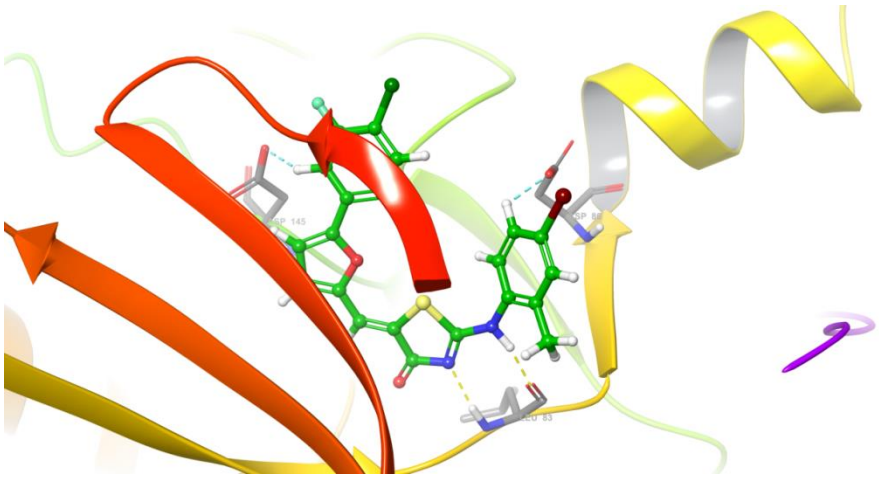


Figure 2: Docking Pose of 10c on CDK2

Besides, leucine deprivation in breast cancer has been reported to inhibit cell proliferation and induce apoptosis.

Despite the fact that many interactions are seen, it may be the cause of target protein inhibition.

Chapter 6: *In vitro* and *in vivo* evaluation of newly synthesized compounds

In vitro studies

In vitro studies are performed in cells isolated either freshly from organ or from cell or tissue culture. This kind of study is widely used in cellular and molecular biology, biochemistry, biotechnology, pharmacology and toxicology. However, this type of study is very economic and does not require ethical clearance and provides a mechanistic data. On the other hand, *in vitro* models exclude the real setting of a living organism. During *in vitro* experiments, some mechanisms on drug action could not be predicted. This could be due to hormonal, nutritional factors, heterogeneity and interaction with the cells [46].

During this research work, about thirty compounds have been screened for their antibacterial, anticancer and anti-inflammatory activities. The said biological screenings have been done based on *in silico* results for each synthesized scheme. Aminothiazole derivatives have been docked in the active pocket of *E. coli* FabH (PDB: 2VBA) and so antibacterial screening was performed. Thiazolidinone and thiazolidinedione derivatives have the same moiety and so have been docked with the same enzyme CDK2 (PDB: 3QQK) and were screened for anticancer activity. However, anti-inflammatory activity has been done as additional activity on these last two schemes.

***In vivo* studies**

Even though running experiments in humans minimizes the risk of getting irrelevant responses, it is absolutely unethical and infeasible as the undesirable reactions of a given compound are not completely reliable. Scientists are forced to use different animal models. Accordingly, animal-based experiments elevated ethical concerns. However, the results from *in vivo* studies do not give an assured estimation of the activity and fate of given chemical in humans. An example from rats as model of humans can be seen in body weight/body volume ratio and biokinetic properties (absorption, distribution, metabolism and excression patterns). Under *in vivo* condition, some chemicals may accumulate in organs or tissues resulting in prolonged exposure of organism [47]. However, the *in vivo* experiments using animal models could reveal the fate of a drug molecule in the body and which could be related to humans. In this case, the compound 2-[(4-Bromo-2-methylphenyl)amino]-5-{[5-(4-chloro-3-fluorophenyl)furan-2-yl]methylene}thiazol-4(5H)-one (**10c**), the most potent has been taken for *in vivo* work in zebrafish model.

The thiazole compounds (**5a-k**) were screened for their antibacterial activity, *in vitro* by broth dilution assay. All the compounds were tested for their preliminary cytotoxicity by hemolysis assay.

All in all, this work is based on the design, synthesis, characterization and antibacterial screening of novel aminothiazole derivatives as FabH inhibitor [*β*-ketoacyl -ACP synthase (KAS)] which plays major role in bacterial cell wall construction. The compound **5d** had crystallized in monoclinic, *P21/c* space group which was determined by single-crystal X-ray crystallography. *In vitro* antibacterial activity studies were carried out on *S. aureus* (MCC 2043), *E. faecalis* (MTCC 2729), *E. coli* MTCC 443 and *C. violaceus* (MCC 2216). Most of the compounds showed potent inhibition activity against Gram-negative bacteria than Gram-positive bacteria. Compound **5a** showed the highest zone of inhibition of 16 mm and MIC value of 5.33μM which was comparable to that of the standard antibiotic, streptomycin. This result was ably complimented by *in silico* studies where compound **5a** exhibited high affinity, strong binding energy and docking score of 6.214 kcal mol^{-1}. By hemolysis assay, the compounds (**5a**, **5b**, **5c**, **5e** and **5j**) were nonhemolytic and nontoxic to mammalian cells.

The synthesized thiazolidinone compounds (**10a-f**) were screened for their *in vitro* anticancer activity using MTT cytotoxicity assay. Further, they were screened for anti-inflammatory activity by protein inhibition (*in vitro).* During the process of this scheme, the level of

apoptosis and antiangiogenesis of the most potent compound (**10c**) in zebrafish were checked and confirmed that the compound (**10c**) induces apoptosis in zebrafish p53 mutant and inhibits angiogenesis as well.

The synthesized thiazolidinedione compounds (1**5a-f**) & (1**6a-e**) were screened for their *in vitro* anticancer activity by MTT assay and anti-inflammatory activity by protein inhibition. *In silico* study was done by molecular docking analysis. Among the synthesized compounds, (1**5a**, **15b** and **16d**) were found to be potent.

However, all the compounds were tested for their preliminary cytotoxicity by hemolysis assay.

References

1. V.R. Pattabiraman, J.W. Bode, Rethinking amide bond synthesis. *Nature* **2011**, 480, 471.
2. E. Alizadeh, L. Sanche, Precursors of solvated electrons in radiobiological physics and chemistry. *Chem. Rev.*, **2012**, 112, 5578. M. Schnürch, B. Waldner, K. Hilber, M.D. Mihovilovic, *Bioorg. Med. Chem. Lett*., **2011**, 21, 2149.
3. M. Schnürch, B. Waldner, K. Hilber, M.D. Mihovilovic, Synthesis of 5-arylated N-arylthiazole-2-amines as potential skeletal muscle cell differentiation promoters. *Bioorg. Med. Chem. Lett*., **2011**, 21, 2149.
4. N. Siddiqui, M.F. Arshad, W. Ahsan, M.S. Alam, Thiazoles: a valuable insight into the recent advances and biological activities. *Int. J. Pharm. Sci. Drug Res.,* **2009**, 1, 136.
5. K.D. Hargrave, F.K. Hess, J.T. Oliver, N-(4-substituted-thiazolyl) oxamic acid derivatives, new series of potent, orally active antiallergy agents) *J. Med. Chem.,* **1983**, 26, 1158.
6. W.C. Patt, H.W. Hamilton, M.D. Taylor, M.J. Ryan, D.G. Taylor, Structure-activity relationships of a series of 2-amino-4-thiazole-containing renin inhibitors, *J. Med. Chem.,* **1992**, 35, 2562.
7. R.N. Sharma, F.P. Xavier, K.K. Vasu, S.C. Chaturvedi, S.S. Pancholi, Synthesis of 4-benzyl-1, 3-thiazole derivatives as potential anti-inflammatory agents: an analogue-based drug design approach, *J. Enzyme Inhib. Med. Chem.,* **2009**, 24, 890.
8. J.C. Jean, L.D. Wise, B.W. Caprathe, H. Tecle, S. Bergmeier, 4-(1, 2, 5, 6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines: A novel class of compounds with central dopamine agonist properties, *J. Med. Chem.,* **1990**, 33, 311.
9. K. Tsuji, H. Ishikawa, Synthesis and anti-pseudomonal activity of new 2-isocephems with a dihydroxypyridone moiety at C-7, *Bioorg. Med. Chem. Lett.,* **1994**, 4, 1601.
10. F.W. Bell, A.S. Cantrell, M. Hogberg, S.R. Jaskunas, N.G. Johansson, Phenethylthiazolethiourea (PETT) Compounds, a New Class of HIV-1 Reverse Transcriptase Inhibitors. 1. Synthesis and Basic Structure-Activity Relationship Studies of PETT Analogs, *J. Med. Chem.,* **1995**, 38, 4929.
11. N. Ergenc, N, G. Capan, N.S. Gunay, S. Ozkirimli, M. Gungor, S. Ozbey, E. Kendi, Synthesis and Hypnotic Activity of New 4-Thiazolidinone and 2-Thioxo-4, 5-imidazolidinedione Derivatives, *Arch. Pharm. Pharm. Med. Chem.,* **1999**, 332, 343.

12. L. Duan, Y. Hong, C. Jia, Y. Li, Design and discovery of 2-(4-(1H-tetrazol-5-yl)-1H-pyrazol-1-yl)-4- (4-phenyl)thiazole derivatives as cardiotonic agents via inhibition of PDE3, *Bioorgan. Med. Chem.*, **2015**, 23, 6117.
13. T. S. Griffin, Thioureas in the synthesis of heterocycles, *Adv. Heterocyclic Chem.*, **1975**, 18, 109.
14. M. Khan, S. Hameed, T. Akhtar, N. Masoudi, W. Masoudi, P. Jones, C. Pannecouque, Synthesis, crystal structure, anti-HIV, antiproliferative activity of new oxadiazole and thiazole analogs, *Med. Chem. Res*., **2016**, 25, 2409.
15. J. Harnett, V. Roubert, C. Doro, C. Charnet, B. Spinnewyn, S.Cornet, J. Marin, D. Bigg, P, Chablier, Phenolic thiazoles as novel orally-active neuroprotective agents, *Bioorg. Med. Chem. Lett*., **2004**, 14, 160.
16. F. Azam, A.I. Alkskas, A.M. Ahmed, Synthesis of some urea and thiourea derivatives of 3-phenyl/ethyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidine and their antagonistic effects on haloperidol-induced catalepsy and oxidative stress in mice, *Eur. J. Med. Chem.*, **2009**, 44, 3889.
17. C. Mishra, S. Kumari, M.Tiwari, Thiazole: A promising heterocycle for the development of potent CNS active agents, *Eur. J. Med. Chem*, **2015**, 92, 34.
18. B. Ghosh, T. Antonio, P. Kharkar, M. Reith, A. Dutta, Development of (S)-N^6-(2-(4-(isoquinolin-1-yl)piperazin-1-yl)ethyl)-N^6-propyl-4,5,6,7tetrahydrobenzo[*d*]-thiazole-2,6-diamine and its analogue as a D3 receptor preferring agonist: potent *in vivo* activity in Parkinson's disease animal models, *J. Med. Chem*, **2010**, 53, 1037.
19. Robert E. Buntrock, Review on heterocyclic chemistry, 5th edition, *J. Chem. Educ*., **2012**, 89, 1350.
20. The Chemistry of Heterocycles, T. Eicher, S. Hauptmann,; Wiley-VCH: Weinheim, Germany, **2003**.
21. R. K. Bonsal, Heterocyclic Chemistry, 3rd ed; New age international publishers: New Delhi, India, **1999**.
22. K. Omar, A. Geronikaki, P. Zoumpoulakis, C. kamoutsis, M. Sokovic, A. Ciric, J. Glamoclija, Novel 4-thiazolidinone derivatives as potential antifungal and antibacterial drugs, *Bioorg. Med. Chem*, **2010**, 18, 432.
23. F. Aydogan, C. Yolacan, Transformations of Aldimines Derived from Pyrrole-2-carbaldehyde. Synthesis of Thiazolidino-Fused Compounds, *Bull. Korean. Chem. Soc*. **2001,** 22, 476.

24. P. Manojkumar, G. Subbuchettiar. Synthesis of coumarin heterocyclic derivatives with antioxidant activity and in vitro cytotoxic activity against tumour cells, *Acta. Pharm.* **2009,** 59, 159.

25. S. Jubie, B. Gowramma, N, Jawahar, R. Kalirajan, S. Gomathy. Synthesis and biological evaluation of some 3-(methoxy phenyl)-2-aryl-thiazolidin-4-one derivatives *Ind. J. Pharm. Sci*. **2009,** 1, 32.

26. B. Goel, T. Ram, R. Tygi, E. Bansal, A. Kumar, D. Mukherjee. 2-Substituted-3-(4-bromo-2-carboxyphenyl)-5-methyl-4-thiazolidinones as potential anti-inflammatory agents, *Eur. J. Med. Chem.* **1999**, 34, 265.

27. M. Chaturvedi, S. Parmar, SK.Chaudhary, AK. Chaturvedi, BV. Ramasastry, **CNS** depressant activity of pyrimidylthiazolidinones, *J. Pharm. Sci.* **1976**, 64, 443.

28. D. Sriram, P. Yogeeshwar, A. Kumar, Microwave-assisted synthesis and anti-YFV activity of 2, 3-diaryl-1, 3-thiazolidin-4-ones, *J. Pharm. Sci*. **2005,** 8, 426.

29. R. Rawal, 2-(Aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT inhibitors, *Bioorg. Med. Chem.* **2005**, 13, 6771.

30. A. Saeed, N. Abbas, U. Florks, Synthesis and antibacterial activity of some novel 2-aroylimino-3-aryl-thiazolidin-4-ones, *J. Braz. Chem. Soc.* **2007**, 18, 559.

31. N. Terzioolu, N. Karaly, Synthesis charecterization and biological activity of some pyrimidine derivatives, *Arkivoc*. **2006**, 2, 109.

32. S. Jubie, B. Gowramma, K. Nitin, K. Elango, Synthesis and Antimicrobial Evaluation of some 2-Azetidinone derivatives, *Int. J. Chem. Tech. Res*. **2009**, 1, 153.

33. S. Jiwane, V. Singh, K. Namdeo, Synthesis of some novel 2, 4-thiazolidinedione derivatives and their biological screening as antidiabetic agents, *As. J. Chem*, **2009**, 7, 5068.

34. D. Sriram, P. Yogeeswar, K. Madhu, Synthesis and in vitro antitubercular activity of some1-[(4-sub)phenyl]-3-(4-{1-[(pyridine-4carbonyl)hydrazono]ethyl}phenyl)thiourea, *Bioorg. Med. Chem. Lett*, **2006**, 16, 878.

35. S. Holla, V. Malini, S. Rao, B. K. Sarojini, S. Kumari, Synthesis of some new 2,4-disubstituted thiazoles as possible antibacterial and anti-inflammatory agents, *Eur. J. Med. Chem*, **2003**, 38318.

36. N. Obushak, Y. Gorak, V. Matiishuk, R, Lytvyn, Synthesis of Heterocycles Based on Arylation Products of Unsaturated Compounds: XVII.* Arylation of 2-Acetylfuran and

Synthesis of 3-R-6-(5-Aryl-2-furyl)- 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines, *Russ. J. Org*, **2008**, 44, 1694.

37. D. Kaminskyy, D. Khyluk, O. Vasylenko, L. Zaprutko, R. Lesyk, A facile synthesis and anticancer activity evaluation of spiro [thiazolidinone-isatin] conjugates**,** Sci.Pharm, **2011**, 4, 777.
38. D. Obushak, I. Gorak, S. Matiichuk, Z. Lytvyn, A simple and convenient synthesis of 3-arylpyran-2-ones via the Meerwein reaction**,** *Russ. J. Org*, **2008**, 11, 1694.
39. H. Chen, Y. Fan, A.Natarajan, Y. Guo, J. Iyasere, F. Harbinski, L. Luus, W. Christ, H. Aktas, J. Halperin, Synthesis and biological evaluation of thiazolidine-2, 4-dione and 2, 4-thione derivatives as inhibitors of translation initiation**,** *Bioorg. Med. Chem. Lett*, **2004**. 14, 5405.
40. Impact, version 2.3, Schrodinger, LLC, New York, **2009**.
41. Impact, version 5.5, Schrodinger, LLC. New York, **2005**.
42. Schrodinger Suite 2009 Protein Preparation Wizard; Epik version 2.0 Schrodinger, LLC, New York, **2009**.
43. Glide, version 5.5, Schrodinger, LLC, New York, **2009**.
44. Raissa, K.C.; Jamerson, F.; Moreira, H.A.; Pinto, O.G.; Camargo, L.T.; Naves, P.L.; Camargo, A.J.; Ribeiro, L.; Ramos, L.M, Synthesis, antimicrobial activity and structure-activity relationship of some 5-arylidene-thiazolidine-2,4-dione derivatives. *J. Braz. Chem. Soc*, **2019**, 30, 164-172.
45. Bombardieri, C.C.; Taurins, A,. The mannich condensation of compounds containing acidic imino groups. *Can. J. Chem*. **1955**, *33*, 923-928.
46. N. Chandra, Expert. Computational systems approach for drug target discovery, *Opin. Drug. Discov*. **2009**, 4, 1236.
47. V. C. Guido, G. Oliva, D. Adriano. Modern drug discovery technologies: opportunities and challenges in lead discovery, *Curr. Med. Chem*, **2008**, 15, 46.

LIST OF PUBLICATIONS

List of Research Papers Published in Journals and Presented in Conferences

1. **Nadine Uwabagira.**, B. K. Sarojini., Prabhu Ashwini., Synthesis, *in vitro* anticancer, anti-inflammatory and DNA binding activity of thiazolidinedione derivatives. Anti-Cancer Agents in Medicinal Chemistry, **2020**. **DOI: 10.2174/1871520620666200424102615**.

2**. Nadine Uwabagira.**, B. K. Sarojini., Madan. S. Kumar, Ramesh S. Gani., Potent pharmacophoric aminothiazole derivatives as FabH inhibitors for antibacterial activity: *In vitro* and *in silico* approach. SN Applied Sciences, **2019**. **DOI: 10.1007/s42452-019-1298-2.**

3. **Nadine Uwabagira.**, B. K. Sarojini., 3-{[(2,3-Dichlorophenyl)amino]methyl}-5-(furan-2-ylmethylidene)-1,3-thiazolidine-2,4-dione. Molbank, **2019**. **DOI: 10.3390/M1083**

4. **Nadine Uwabagira.,** B. K. Sarojini., Boja Poojary., *4*-(4-fluorophenyl)-*N*-(4-nitrophenyl) thiazol-2-amine. Molbank, **2018**. **DOI: 10390/M975**.

5. **Nadine Uwabagira**, B. K. Sarojini, Exploring thiazolidinone derivative for anti-breast cancer activity using structure based drug designing" Presented at three days "International conference on "Current concepts on the role of Indian medicine and phytoceuticals in maintenance of health (39th IABMS-2018)" organized by Department of Studies and Research in Biochemistry, Post Graduate Centre, Jnana Kaveri, Chikka Aluvara, MANGALORE UNIVERSITY, held during November 15-17, 2018.

6. **Nadine Uwabagira**, B. K. Sarojini, Synthesis and characterization of novel thiazolidinedione derivative as potent anticancer agent. Presented at three days International Conference on Radiation Biology (ICRB) 2018 organized by NITTE DEMED TO BE UNIVERSITY, Mangalore, held during October, 04-06, 2018.

7. **Nadine Uwabagira**, B. K. Sarojini, Jean Baptist Nkurunziza, 2-aminothiazole derivatives as inhibitors of penicillin binding proteins: Design, synthesis and characterization. Presented at three days International Conference on Emerging Trends in Chemical Sciences (ICETCS) organized by MANIPAL INSTITUTE OF TECHNOLOGY (MIT), held during September 14-16, 2017.

8. **Nadine Uwabagira**, B. K. Sarojini: Design, synthesis, characterization and molecular docking studies of new series of 2-anilinothiazole derivatives as potent anti-inflammatory agents. Presented at two days National Conference on "Reaching the Unreachable through Science and Technology": Recent Advances in Physical, Chemical, Mathematical and Biological Sciences for Energy, Health and Environment" organized by MANGALORE UNIVERSITY, Mangalagangothri, held during September 8-9, 2017.

Uwabagira Nadine
(Research Student)

Date:

Dr. B. K. Sarojini
(Research Guide)

Date: